



Original Research Article

## A Prospective Study Comparing Talc and Tetracycline Pleurodesis in Pneumothorax

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### ABSTRACT

**Background:** There is a significant rate of recurrence of both primary and secondary pneumothoraces, and efforts to reduce recurrence by instilling various sclerosants are often undertaken. Tetracycline used to be recommended as the first line sclerosant therapy for both primary and secondary pneumothoraces. Graded talc has also been used on the grounds that it is the most effective agent in treating malignant pleural effusion but its efficacy in pneumothorax is not clear.

**Aims and Objectives:** To find out the success rate of talc and tetracycline pleurodesis in preventing recurrence of pneumothorax and to find out the incidence and complications in each group.

**Materials and methods:** Patients were randomised using standard randomisation table to receive either talc or tetracycline pleurodesis. 30 patients were included in the study. 15 patients underwent talc pleurodesis and 15 patients underwent tetracycline pleurodesis. After pleurodesis, patients were followed up for 1 year.

**Results:** 12 out of 15 patients who underwent tetracycline pleurodesis had no recurrence (success rate=80%) and 13 out of 15 patients who underwent talc pleurodesis had no recurrence (success rate=86.66) within 1 year. Recurrence rate for tetracycline was 1.5 times that for talc but the difference was found to be statistically insignificant ( $p$  value=0.62). The complication profile in both groups was also comparable.

**Conclusion:** In this study no significant difference was found between talc and tetracycline used as sclerosants for pleurodesis in preventing recurrence of pneumothorax and the complications encountered. Tetracycline appears to be more cost effective than talc (graded talc is 100 times costlier than tetracycline in India).

**Key words:** Pleurodesis, Pneumothorax, Talc, Tetracycline, Talc poudrage, Talc slurry.

**MeSH terms:** Pleurodesis, Pneumothorax, talc, tetracycline.

### INTRODUCTION

Pleurodesis is the installation of substances into the pleural space leading to an aseptic inflammation, with dense

adhesions leading ultimately to pleural symphysis. There is a significant rate of recurrence of both primary and secondary pneumothoraces, and efforts to reduce

recurrence by instilling various sclerosants - either via a chest drain, or VATS, or open surgery - are often undertaken without clear guidelines to direct physicians in their use. Many sclerosing agents suitable for installation into the pleural space have been studied. Tetracycline used to be recommended as the first line sclerosant therapy for both primary and secondary pneumothoraces, as it proved to be the most effective sclerosant in animal models. [1-3] Recently, however, parenteral Tetracycline for pleurodesis has become more difficult to obtain due to problems with the manufacturing process. Minocycline and Doxycycline have also been shown to be reasonable alternative sclerosing agents in animal model. Chemical pleurodesis using graded talc is an effective alternative to Tetracycline pleurodesis, but there are no controlled trials comparing the two in the treatment of pneumothorax. The rate of recurrence of pneumothorax is the primary indicator for success for any recurrence prevention techniques.

**Aims and objectives:**

The aim of this study is to find out the success rate of talc and tetracycline pleurodesis in preventing the recurrence of pneumothorax and to find out the incidence of complications in each group.

**MATERIALS AND METHODS**

**Study setting:**

Patients admitted to Institute of chest diseases, Calicut medical college with pneumothorax- requiring pleurodesis according to clinical decision.

**Study period:**

January 2011 to Oct 2012 (including follow up period)

**Type of study:**

Randomised control study - randomised using standard randomisation table

**STUDY CRITERIA:**

**Inclusion criteria:**

1. Ipsilateral recurrence
2. Contralateral occurrence
3. Bilateral pneumothorax
4. 1st life threatening attack of pneumothorax
5. Patients with underlying severe lung diseases
6. High risk professions- pilots and divers

**Exclusion criteria:**

1. Patients on long term immune-suppressants or anti-inflammatory drugs
2. Patients with immunosuppressive diseases
3. Traumatic pneumothorax
4. Patients not willing for pleurodesis
5. Previous ipsilateral failed pleurodesis

**Scheme:**

Each patient was randomly allotted to either talc or tetracycline pleurodesis-using random number table.

**Procedure:**

The study was started after obtaining the Institutional Ethical Committee clearance. Patients admitted with pneumothorax in the Institute of Chest Diseases were evaluated clinically and radiologically. Where indicated tube thoracostomy was done in patients according to BTS guidelines (2009). Patients who require pleurodesis were chosen according to the inclusion criteria mentioned above. Written informed consent was taken. And the pleurodesis agent was chosen according to the random number table. Pleurodesis was done once full lung expansion was achieved. If the patient was on steroids they were stopped 24-36 hours before the procedure. 4 gram of talc or 1500 mg<sup>4</sup> of tetracycline was used. The tube was clamped at the proximal portion of the tube near the insertion site with the patient lying in supine position. Part of the tube proximal to the clamped site was cleaned with spirit to make it sterile. Then 250mg of lignocaine was injected through the tube into the pleural cavity to provide analgesia. 4g of sterile talc mixed with 30 ml of sterile

normal saline or 1500mg of oxytetracycline was injected through the tube followed by injection of 50-100 ml of sterile normal saline for even distribution of the sclerosing agent. In case of talc poudrage the procedure was done using medical thoracoscopy. The tube was kept clamped for 2 hours and the patient was asked to change position frequently. Clamp was then removed after 2 hours. If the patient complained of pain inj. Tramadol was given. The tube was removed after assessing the patient clinically and radiologically. Any complication like fever, pain or infection was noted. A temperature of >38 C was taken as fever. Pain which required a dose of analgesic was considered as significant. Pleural fluid was sent for culture in patients who had fever. Culture positivity was taken as presence of infection. The patient was then followed up on an OPD basis.

**Follow up:**

- 1st visit- 2weeks after discharge.
- 2nd visit- at 2 months.
- 3rd visit - at 6 months.
- 4th visit – at 12 months.

On every visit the patient was assessed clinically and with a fresh chest X-ray. Any patient who had recurrence in between was not followed up further. The success rate of each of the sclerosing agent was then calculated with the number of recurrences occurring with each agent.

**Success criteria:**

Pleurodesis was considered successful when the patient who underwent pleurodesis using a particular agent did not develop recurrence of pneumothorax on the same side after 1 year and the success rate was calculated accordingly for each agent separately.

**Statistical analysis:**

Statistical analysis was done using SPSS software (version 16). Chi square test was used to compare categorical variables. Independent sample t test was used to

compare the mean of two groups. P value <0.05 was taken as significant.

**RESULTS**

A total of 30 patients were included in the study. Of which 15 underwent tetracycline pleurodesis and 15 underwent talc pleurodesis after getting informed consent. All 30 patients were males.

**Demography:**

The mean age, mean BMI, mean height and the mean smoking index were all comparable between both groups (Table 1).

**Table 1: Comparison of Demographic data in talc and tetracycline groups**

Variable	Talc	Tetracycline
Mean Age(years)	53.2	54.67
Mean BMI	19.31	18.83
Mean Height(cm)	167.2	165.47
Smoking Index (mean)	660	635

**Underlying lung condition:**

27 out of 30 patients had underlying COPD. 2 of them had no underlying lung diseases (i.e., they had primary spontaneous pneumothorax). One patient had underlying malignancy. Out of the 27 COPD patients 7 had underlying bulla as evidenced by chest X- rays or in few cases by CT-Thorax.

**Success rate:**

2 out of 15 patients who underwent talc pleurodesis had recurrence and 3 out of 15 patients who underwent tetracycline pleurodesis had recurrence. The success rate for talc pleurodesis is 86.7% and for tetracycline pleurodesis it is 80%. One patient in the tetracycline group had underlying malignancy and died during follow up. For analysis purposes it was taken as recurrence. The difference in success rate between two groups was not found to be statistically significant [p:1.00].

## Complications:

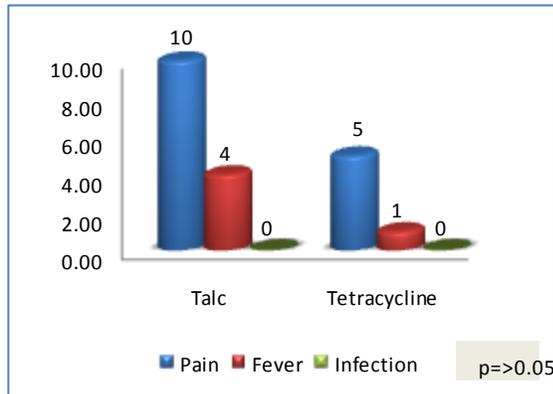


Figure1: Comparison of complications in the two groups.

Three important recognized complications of pleurodesis were compared between both groups. They are pain, fever and infection. In general, talc pleurodesis lead to more complications than tetracycline (see Figure 1). But the difference was statistically insignificant ( $p > 0.05$ ).

## Duration of drain:

The mean duration of drain was 1.6 days in talc group and 1.27 days in tetracycline group. The difference was not found to be statistically significant. [ $p: 0.216$ ]

## Talc poudrage:

2 patients underwent talc poudrage using medical thoracoscopy.

- ❖ Success rate: 100%
- ❖ Complications:
  1. Pain: 100% (both had pain)
  2. Fever: 50% (1 had fever)
  3. Infection: nil
- ❖ Mean duration of drain: 3 days

## Factors affecting success rate:

### 1) Agent (Table 2):

Table 2 : Recurrence rates in each group

	Recurrence Yes	Recurrence No	p value
Talc	2 (13.3%)	13 (86.7%)	0.623
Tetracycline	3 (20%)	12 (80%)	

The difference was not found to be statistically significant ( $p$  value: 0.623)

### 2) Age:

Mean of 55 was taken to categorise age. 15 patients belonged to age category  $> 55$  of which 1 patient developed recurrence. 15 patients belonged to age category  $\leq 55$  of which 4 developed recurrence. But the  $p$  value (0.33) was not found to be significant.

### 3) BMI:

21 was taken as a cut off to categorize BMI since according to BODE index a BMI of  $\leq 21$  is a predictor of mortality in COPD patients and since most of our patients were also COPD. Recurrent primary spontaneous pneumothorax is also common in tall, thin individuals. 2 out of 8 patients in BMI category  $> 21$  developed recurrence and 3 out of 22 patients of BMI category  $\leq 21$  developed recurrence. The difference was not found to be statistically significant [ $p$  value: 0.589]

### 4) Underlying lung condition (Table 3):

Table 3: Underlying lung condition and recurrence rates

Risk factor	Recurrence		p value
	Yes	No	
COPD	5 (18.5%)	22 (81.5%)	1.000
Underlying bulla	3 (42.9%)	4 (57.1%)	0.068

27 out of 30 patients included in the study had underlying COPD of which 5 developed recurrence. [ $p$  value: 1.00] 7 out of the 27 COPD patients had underlying bulla as evidenced by radiography of which 3 developed recurrence. [ $p$  value: 0.068]

### 5) Smoking history:

28 patients out of 30 patients included in the study were smokers of which 5 developed recurrence. 2 were nonsmokers. Both didn't develop recurrence. The difference was not found to be statistically significant. [ $p$  value: 1.00].

**6) Previous history of pneumothorax:**

25 out of 30 patients included in the study had previous history of pneumothorax of which 4 developed recurrence after pleurodesis. 5 patients had no previous history of pneumothorax of which 1 developed recurrence after pleurodesis. The difference was not found to be statistically significant [p value: 1.00].

**7) Primary/secondary spontaneous pneumothorax:**

2 out of 30 patients in the study had primary spontaneous pneumothorax of which none developed recurrence after pleurodesis. 28 patients had secondary spontaneous pneumothorax of which 5 developed recurrence after pleurodesis. But the [p value: 1.00] was not found to be significant.

**Recurrence time:**

Out of the 5 patients who developed recurrence-

- a) 2 patients developed recurrence within 1 week of pleurodesis. (1 had talc and 1 had tetracycline pleurodesis),
- b) 2 patients developed recurrence within 2 weeks of pleurodesis. (1 had talc and 1 had tetracycline pleurodesis) and
- c) 1 patient died during follow up at 6 months. He had undergone tetracycline pleurodesis. Until 6 months he didn't develop recurrence. He had underlying malignancy. For analysis purposes this case was considered as a case of recurrence as definite outcome could not be established.

**DISCUSSION**

Recurrence is an important complication of spontaneous pneumothoraces which contributes to the morbidity in these patients. Various surgical and nonsurgical methods have been tried to

minimize recurrence. Surgical methods are the method of choice if available.

In patients in whom surgery is not an option medical chemical pleurodesis is an acceptable option to prevent recurrence. Many sclerosing agents suitable for installation into the pleural space have been studied. Tetracycline used to be recommended as the first line sclerosant therapy for both primary and secondary pneumothoraces, as it proved to be the most effective sclerosant in animal models. [1-3] Recently, however, parenteral Tetracycline for pleurodesis has become more difficult to obtain due to problems with the manufacturing process. Graded talc has been used on the grounds that it is the most effective agent in treating malignant pleural effusion, and is also commonly used for surgical chemical pleurodesis. [4] Chemical pleurodesis using graded talc is an effective alternative to Tetracycline pleurodesis, but there are no controlled trials comparing the two in the treatment of pneumothorax. Most of the studies related to talc has been in cases of pleural effusion. But it has also been used in recurrent pneumothoraces. The rate of recurrence of pneumothorax is the primary indicator for success for any recurrence prevention techniques. Our aim was to compare the success rate of talc and tetracycline pleurodesis in patients with pneumothorax and to compare the complication profile of both group.

The study was started after getting the approval of The Institutional Ethics Committee. After getting informed consent 30 patients were included in the study of which 15 underwent talc pleurodesis and 15 underwent tetracycline pleurodesis. Most of the patients had underlying COPD (27 out of 30), 2 patients had recurrent primary spontaneous pneumothorax and one patient had underlying malignancy (disseminated malignancy with b/l lung metastasis). 7 out of the 27 COPD patients had underlying

bullae as evident by chest x-ray or in some cases by CT-Thorax. A total of 5 patients had recurrence- 2 in talc group and 3 in tetracycline group.

### **SUCCESS RATE:**

#### **Tetracycline pleurodesis:**

Alfagemeet al <sup>[2]</sup> conducted a study from 1985 to 1991 in which 78 patients with spontaneous pneumothorax underwent tetracycline pleurodesis. Follow up period in this study was 45 months (average). It showed that the recurrence rate for tetracycline pleurodesis in patients with spontaneous pneumothorax was around 9 %. And the recurrence time ranged from 2 days to 9 months.

Another study was conducted by Merete Almindet al <sup>[5]</sup> from 1978 to 1985. In this study 96 patients with spontaneous pneumothorax were randomised into three groups, receiving either treatment with simple drainage (34 patients), drainage with tetracycline pleurodesis (33 patients), or drainage with talc pleurodesis (29 patients). The incidence of recurrence was 36% in the simple drainage group, 13% in the tetracycline pleurodesis group, and 8% in the talc pleurodesis group.

In our study we had a recurrence rate of 20 % for tetracycline pleurodesis. i.e., 3 out of 15 patients had recurrence. The higher recurrence rate in our study could be due to the smaller sample size.

#### **Talc pleurodesis:**

The success rate of talc pleurodesis in pneumothorax have varied from 31% to 100%. And the dose used has also varied in different studies. While talc slurry has been used with success in the treatment of pneumothorax, poudrage at the time of thoracotomy, thoracostomy, and pleuroscopy is by far the most common method of administration. The overall success rate is 91 percent.

In our study the success rate for talc pleurodesis was 86.7 %. i.e., 2 out of 15 patients who underwent talc pleurodesis developed recurrence. 2 of them underwent talc poudrage using medical thoracoscopy. The success rate in our study was comparable to previous studies.

A study by Merete almind et al <sup>[5]</sup> showed a recurrence rate of 8% in the talc pleurodesis group.

Talc appears to have higher success rate compared to tetracycline pleurodesis in our study but the p value was not significant showing that there was no significant difference between both groups in terms of recurrence. Since talc is much costlier than tetracycline the latter appears to be more cost effective in preventing recurrence in pneumothorax. Underlying bullae was found to be a significant risk factor for recurrence after pneumothorax. 3 out of the 7 patients who had underlying bullae had recurrence.

#### **Complications:**

There are 3 important recognized complications of pleurodesis. They are pain, fever and infection. Most pleurodesis agents are associated with pain at the time of instillation into the pleural space. Walker-Renard and colleagues <sup>[6]</sup> reported pain with talc in 9 of 131 (7 percent) patients. Fever following pleurodesis is common and has been noted following the administration of most agents <sup>[7]</sup> Fever following talc poudrage and slurry is common, occurring from 16 to 69 percent of the time. Fever characteristically occurs 4 to 12 h following talc instillation and may last for 72 h.

Empyema and ARDS have been reported in talc pleurodesis but these are rare when sterile graded talc is used. For tetracycline pleurodesis, the most commonly reported adverse effects were pain and fever.

In our study pain was found in 66.7% (10 out of 15 patients) in the talc group. And fever was seen in 26.7 % (4 out

of 15 patients) which was comparable to other studies. The incidence of pain (2/2 patients) and fever (1/2) was also higher in talc poudrage group.

In our study 33.3% (5 out of 15 patients) in the tetracycline group had pain which was comparable to previous studies. And fever was seen in 6.7% which was slightly lowered comparable to other studies. Possible reason could be due to ethnic and racial differences in the type and magnitude of reaction after pleurodesis. And most of the studies have been conducted using tetracycline. We had used oxytetracycline in our study. A difference in the method of manufacturing the drug oxytetracycline could also be a reason.

The higher incidence of pain and febrile reaction in talc group could be due to intense sterile pleurisy which has been explained in talc pleurodesis. None of our patients who underwent pleurodesis had infection. In all patients who had fever following pleurodesis the drained pleural fluid was sent for culture and it turned out to be sterile in all cases.

Bullous lung diseases and bullous emphysema have been known to produce recurrent pneumothorax. In our study 7 patients had underlying bulla recognized by radiography of which 3 developed recurrence after pleurodesis. This might be due to inadequate pleural reaction at the site of bulla which may be due to some defect in the underlying pleura. This has to be further studied to be validated.

The duration of drain indirectly signifies the magnitude of pleural reaction following pleurisy. In our study, the mean duration of drain does not vary much between the two groups (1.6 days in talc and 1.2 days in tetracycline groups respectively- P value:0.355) though it was higher in patients who underwent talc poudrage(3 days- **p value:0.00**). This could be explained because these patients underwent an

invasive procedure and talc poudrage is known to produce more intense sterile pleurisy.

The smoking habit being associated with a 12% risk of developing pneumothorax in healthy smoking men, compared to 0.1% in non-smokers. In our study 28 patients out of 30 patients included in the study were smokers of which 5 developed recurrence. 2 were nonsmokers. Both didn't develop recurrence. But the difference was not found to be statistically significant.

The risk of recurrence in Primary spontaneous pneumothorax is 39-54% within 1<sup>st</sup> 4 years and in Secondary spontaneous pneumothorax is 16-50% for first recurrence, 40-64% for 2<sup>nd</sup> recurrence and 80% for 3<sup>rd</sup> recurrence. [7-10] This shows that patients who already had recurrence tend to have further recurrences. So analysis was done comparing the number of previous recurrences and recurrence after pleurodesis. 25 out of 30 patients included in the study had previous history of pneumothorax of which 4 developed recurrence after pleurodesis. 5 patients had no previous history of pneumothorax of which 1 developed recurrence after pleurodesis. But the difference was not found to be statistically significant [p:1.00]. And 2 out of 30 patients in the study had primary spontaneous pneumothorax of which none developed recurrence after pleurodesis. 28 patients had secondary spontaneous pneumothorax of which 5 developed recurrence after pleurodesis. But the [p value: 1.00] was not found to be significant.

#### **Recurrence time:**

A study by **Olsen et al** [1] showed that 50% of the recurrences after pleurodesis occurred within 30 days and 82% within 1 year. In our study 4 out of 5 patients who had recurrence had recurrence within first 2 weeks. One patient died after 6 months due to underlying malignancy. The higher rate of

early recurrence seen in our study could be due to the smaller sample size.

### ***Limitations of the study:***

- ❖ Small sample size- only 30 patients were included in the study. We could have obtained significant p values in comparing various variables had we had a good sample size. But we chose a sample size according to the number of cases of recurrent pneumothorax we get in our institution.
- ❖ Single centre study- So the results obtained could only be applicable to people belonging to this part of the country.
- ❖ Most of the patients were COPD.
- ❖ Follow up period-only one year. Following up the patients further would give a more clear idea about the success rate of these pleurodesis agents in the long term.

### **CONCLUSION**

In our study we found that there was no significant difference between talc and tetracycline pleurodesis in terms of success rate in patients followed upto 1 year. Tetracycline seems to be more cost effective. Talc poudrage seems to have superior success rate but we had only 2 patients so a definite opinion is not possible. The complication profile in both groups was also comparable. Even though the incidence of pain and fever was more in talc group it was not disabling and none developed infection.

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